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08/256,631

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18M2/1013

EXAMINER	
GAMBEL, P	
ART UNIT	**PAPER NUMBER**
1816	11

DATE MAILED: 10/13/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 4/10/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-21 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-21 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. If applicant desires priority under 35 U.S.C. § 120 based upon a parent application, specific reference to the parent application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. Status of the parent application (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "Patent No." should follow the filing date of the parent application. If a parent application has become abandoned, the expression "abandoned" should follow the filing date of the parent application.

Applicant should provide the parent applications and their current status on the first line of the specification.

16. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should indicate the specificity of VLA-4 in the title.

17. This application does not contain an Abstract of the Disclosure as required by 37 C.F.R. § 1.72(b). An Abstract on a separate sheet is required.

18. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

19. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

20. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-20 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims (1-20) and (1-19 and 22) of copending application Serial Nos.(08/374,331) and (08/456,193). This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

22. Claim 21 is provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims (21), (20,21), (20), (20) and (20) of copending application Serial Nos. (08/374,331), (08/456,193), (08/284,603), (08/373,857), (08/456,124), respectively. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented. The claimed inventions are drawn to pharmaceutical compositions consisting essentially of VLA-4-specific antibodies.

A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant would be inherent properties of the referenced antibodies.

A pharmaceutically acceptable carrier such as PBS was well known in the art as solvent for immunoglobulins for storage as well as immunoassays.

In the possibility that there is an embodiment of the invention that falls within the scope of one claim but not the other; the identical subject matter is not defined by both claims and statutory double patenting would not exist.

It is noted that these claims are composition rather than compound claims, therefore it is possible that the pharmaceutically acceptable carrier may differ between treating asthma (instant 08/256,631, 08/374,331, 08/456,193) and inflammatory bowel disease (08/284,603, 08/373,857, 08/456,124).

Claim 21 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (20), (20) and (20) of copending application Serial Nos. (08/284,603), (08/373,857) and (08/456,124). Although the conflicting claims are not identical, they are not patentably distinct from each other because each composition is drawn to the same active ingredient consisting essentially of VLA-4-specific antibody. It would have been obvious to one of ordinary skill in the art at the time the invention was made to place this antibody in the appropriate pharmaceutical carrier for disease targeted.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

23. Claim 12-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23-25 of copending application Serial No. 08/456,193. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are drawn to the use a polypeptide that binds VLA-4 including soluble VCAM-1 polypeptides for treating asthma and the copending application is drawn to soluble VCAM-1 polypeptides which are fusion proteins and bifunctional fusion proteins. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make the copending fusion proteins and bifunctional fusion proteins for their increase half-life and/or valency for pharmaceutical applications.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 12-20 are directed to an invention not patentably distinct from claims 23-25 of commonly assigned USSN 08/456,193 for the reasons set forth above in this section.

Commonly assigned 08/456,193, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was

made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78(c) to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

24. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. The specification is objected to and claims 1-21 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

Applicant has not enabled the breadth of the claimed invention in view of the teachings of the specification. Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

A) Applicant has not disclosed how to use VLA-4-specific antibodies or fragments thereof alone or combination with other adhesion molecule-specific antibodies therapeutically in humans, as the intended invention. There is insufficient information or nexus of the invention with respect to the in vivo operability of VLA-4-specific immunotherapy with respect to applicant's invention.

Pharmaceutical therapies are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs such as antibodies can be species- and model-dependent, it is not clear that reliance on the in vivo inhibition of some aspects of inflammation by the VLA-4- (α4-) specific antibody HP1/2 in the experimental in vivo experimental asthma animal sheep model accurately reflects the relative efficacy of the claimed therapeutic methods and compositions, encompassed by the instant invention.

With respect to antibody therapy in general, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3)(Tibtech, 1993; 1449, #DB). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences. Antibodies directed against cell-bound antigens would be expected to be more immunogenic than those binding to soluble antigens. It is well known in the art that the clinical efficacy of antibody therapy including humanized antibodies have been limited by specificity, binding constants, tissue penetration, clearance rates and the mode of action of the effector.

Mountain et al. teach that most antibody-based therapies are very unlikely to achieve success with a single dose (Biotech. Gen. Eng. Rev., page 11, paragraph 1, first sentence, 1993). The success of multiple dosing as a therapeutic regimen alleged by applicant is contrary to that experienced in the art. Murine antibodies are limited to one or perhaps two doses and the administration of further doses leads to accelerated clearance and in many cases to complete abrogation of efficacy (Mountain et al., pages 10-11, overlapping paragraph).

In addressing adhesion-based therapy, Harlan states that whether you go humanized antibody, peptide, soluble receptor, or saccharide; it's still a long way to product (Edgington, Biotechnology, 1992; see entire document, particularly page 386, column 3, paragraph 4). The inherent difficulties of this approach include development of serum sickness after injection of foreign protein, diminishing therapeutic effects after prolonged therapy and the potential for promotion of infection.

Ward et al. addresses the current issues associated with the selection of targeting adhesion molecules as an approach to anti-inflammatory therapy (Therapeutic Immunol., 1994; entire document). There are relatively few conditions in which there is clear-cut evidence of the presence and participation of given adhesion molecules in humans (page 166, column 1, paragraph 1). Also, monoclonal antibodies including antigen-binding fragments thereof are not likely to be the ultimate approach for in vivo blocking of adhesion molecules, even though they will likely provide important information (pages 167-170, particularly Concluding Remarks). In addition, it is pointed out that, in spite of extensive development of peptide analogues for various inflammatory mediators and hormones, few if any of these products have found their was to routine clinical application (page 167, column 1, lines 1-23).

Although the animal models validate concepts based on studies of human disease, such studies are limited to the "acute" as opposed to "chronic" nature of the disease. In animal models, the onset of inflammation is rapid with an aggressive destructive process, whereas in humans the disease progresses more slowly, often with natural periods of disease exacerbation and remission. For example, applicant's reliance on the instant allergic sheep model discloses an experimental protocol wherein the HP1/2 antibody is administered one-half hour after the antigen is administered. Amelioration of certain aspects of asthma-associated pathology is much easier to achieve under such controlled conditions to defined antigens associated with the experimental sheep model than that experienced in the human asthma diseases targeted by the claimed invention.

In contrast to highly defined models of asthma relied upon by applicant, human diseases comprise multiple allergens or multiple immune responses that makes therapeutic intervention a major hurdle even for known diseases. Furthermore, it is unclear whether such immunotherapy can be used to treat an ongoing inflammatory or immune response (which is the usual case) or whether it is effective only in terms of prevention. Generally, the chronic and complicated nature of the asthma encompassed by the claims are diagnosed only after significant tissue damage has occurred in contrast the instant sheep model wherein the insult

and therapy are provided essentially at the same time to a naive animal.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based and antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods and compositions are effective for treating asthma.

To obviate this aspect of the rejection, applicant is invited to address the following issues. If applicant's invention does address the use of VLA-4-specific inhibitors for acute reactions rather than a continuous treatment, then this rejection may be obviated. Also, applicant should address that the dosing employed in the instant sheep model wherein the antagonist is administered after the insult would be predictive for alleviating acute allergic reactions.

B) VLA-4 and VLA-α4 comprise multiple receptor-ligand interactions. It is not clear what particular criteria are critical to the VLA-4 or VLA-α4 specificity of the claimed methods and compositions. For example, it is unclear from the specification whether the claimed methods and compositions can be specific for both α4 and β1 subunits of VLA-4. Is the α4 specificity critical or is only certain specific functions or interactions that are critical? VLA-4 can bind both to VCAM and fibronectin. Does one screen for both specificities. Some antibodies block T cell activation others do not.

Does the claimed antibody bind other cell adhesion molecules which comprise α4 but a different β. In turn, is the claimed invention drawn to α4 or certain epitopes of α4, as exemplified by HP1/2, and not necessarily to the broadly claimed VLA-4 specificity per se.

Alternatively, is the β1 specificity a critical aspect of the claimed VLA-4 specificity? If so, similar questions addressed above concerning α4 apply here as well to β1.

In a further variation, does the claimed VLA-4 specificity refer to a linear epitope that is expressed by either the α4 or β1 chain or to a conformational epitope that requires both α4 or β1 chains?

For example, the specification discloses that the preferred VLA-4-specific antibody embodiments bind B1 or B2 epitopes of the α4 chain (pages 9-10 of the specification). Applicant's claim the VLA-4 specificity as well as a plurality of VLA-4 antibodies.

Applicant discloses the use of HP1/2 antibody, which block leukocyte adhesion to VCAM but does not block other VLA-4-mediated functions. It is not clear from the that any VLA-4- or VLA-4α-specificity other than that exemplified by the HP1/2 would serve as candidate therapeutic antibodies. It is not clear that binding and functional attributes of all other VLA-4-specific antibodies or antagonists would be expected to treat asthma.

Furthermore, claims 12-19 are drawn to "a polypeptide or a small molecule capable of binding to the α_4 subunit of VLA-4". These "peptides" or "small molecules" could be any peptide that binds VLA-4 or any soluble carbohydrate that binds VLA-4. Although the specification discloses the use of "a polypeptide or a small molecule capable of binding to the α_4 subunit of VLA-4" for attenuating asthma, there is no evidence provided that such "polypeptides" or "small molecules" would be effective in inhibiting VLA-4-mediated responses associated with asthma either in vitro or in vivo.

Regarding soluble antagonists in adhesion therapy which would be analogous to the instant VLA/VCAM inhibitors; McCabe et al. teach that soluble ICAM-1, enhances cytokine production while ICAM-1-specific and LFA-1-specific antibodies inhibit such activity (Cell. Immunol., 1993; see entire document).

Furthermore, Sherman-Gold reviews the challenges facing cell adhesion molecule-based therapy and indicates that cell adhesion molecules are complex molecules and the regions crucial to their biological activity have not been fully delineated (Gen. Eng. News, 1993, see entire document, particularly page 6, column 5, paragraphs 1-8; 1449, #DA). Therefore, it would be difficult to design small molecules that will be effective in blocking cell adhesion molecules. Other difficulties include the limited potency of a single adhesion pathway in the face of a number of molecules and alternate pathways and the parameters of the appropriate window for beneficial effects without serious side effects. Sherman-Gold also indicated that the low binding affinity of cell adhesion molecules to their counterparts makes screening for small molecules with biological activity less than a clear cut task (see page 6, column 5, paragraph 6).

It is not clear from the specification what are the critical parameters or endpoints by which one could predict the ability of the claimed antagonists to alleviate or treat asthma. Also, the only working example of in vivo treatment is the use of the HP1/2 VLA-4-specific antibody in an experimental sheep asthma model and not the use of any VLA-4-specific antibody (different epitope), antibody fragments, soluble polypeptides or small molecules.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective adhesion-based and antibody-based therapies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods and compositions are effective for treating asthma.

26. The specification is objected to and claim 4 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) sequenced; or (3) deposited.

It unclear if cell lines which produce antibodies having the exact structural and chemical identities of HP2/1, HP2/4, L25 and P4C2 antibodies are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, suitable deposits for patent purposes is suggested. Without publicly available deposits of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell lines; (2) cell line which produce the chemically and functionally distinct antibodies claimed; and/or (3) the claimed antibodies's amino acid or nucleic acid sequences is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar

immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species HP2/1, HP2/4, L25 and P4C2 antibodies. Deposit of the appropriate hybridomas would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

In addition, the identifying information set forth in 37 CFR 1.809 (d) should be added to the specification. See 37 CFR 1.803-1.809 for additional explanation of these requirements.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

It is noted that the provision of SEQ ID NOS 1-4 which encode the claimed HP1/2 antibody obviates a rejection based upon the deposit of this biological material. The HP1/2 antibody is required for the enablement of the claimed invention (claims 4, 5, 13, 16, 20).

27. Claim 14 is rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is indefinite in the recitation of "plurality of anti-VLA-4 monoclonal antibodies" because it is not clear what is meant by this phrase. Does this refer to a plurality of VLA-4 antibodies that bind a single epitope (B1 vs. B2, page 7, paragraph 1 of the specification) or a single antigen (e.g. α4 vs. β1 specificity of VLA-4) or different forms of the same epitope-/antigen-specific antibody (e.g. monoclonal vs. chimeric) or simply more than one antibody molecule. While the specification appears to refer to the use of VLA-4 antibodies, it is not clear what is the antecedent basis with respect to the

metes and bounds of "a plurality of VLA-4 monoclonal antibodies". Only the VLA-4-specific HP1/2 antibody was tested in an asthmatic sheep. For the reasons discussed above in section 21, it is not clear whether any VLA-4-specific antibodies would work therapeutically in asthma observed in humans. Therefore it is not clear from the evidence of record that combinations of different epitope-/ antigen-specific antibodies would work. No clear direction or guidance is provided to assist one skilled in the art in the selection of the appropriate "plurality" of VLA-4-specific antibodies to treat asthma nor is there evidence provided that any such plurality would be therapeutically effective in the treatment of asthma. It appears that undue experimentation would be required of one skilled in the art to practice the claimed methods using the teaching of the specification alone.

If applicant's intention is only to indicate the various antibody forms claimed in claim 12, then "plurality of said anti-VLA-4 monoclonal antibodies" would obviate this rejection.

The amendments must be supported by the specification so as not to add any new matter.

28. Claims 1-21 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-11, 14, 15 and 17-20 are indefinite in the recitation of "composition". Minimally the therapeutically effective amount of the active ingredient and the pharmaceutically acceptable carrier should be recited in the claims. The specific function of the composition may also be included as well.

B) Claims 14, 15 and 17-19 are indefinite in that they lack antecedent basis for "composition".

C) Claim 4 is indefinite in the recitation of "HP2/1, HP2/4, L25 and P4C2" because their characteristics are not known. The use of "HP2/1, HP2/4, L25 and P4C2" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claims indefinite because these terms are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct cell lines.

D) Claims 12-20 are indefinite in the recitation of "chimeric" and "recombinant" antibody because it is not clear what are the metes and bounds of either.

E) Claims 5 and 20 are duplicative of one another and applicant should cancel one or the other.

The amendments must be supported by the specification so as not to add any new matter.

29. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
>
> (f) he did not himself invent the subject matter sought to be patented.

30. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

31. Claim 20 is rejected under 35 U.S.C. § 102(a) as being anticipated by Wayner et al. (WO 91/03252). Wayner et al. teach $\alpha 4\beta 1$-specific antibodies including P4C2 as pharmaceutical compositions (see entire document, particularly page 28-29). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations addressed by the applicant (e.g. for the treatment of asthma) would be inherent properties of the referenced antibodies.

32. Claim 20 is rejected under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Elices et al. (Cell, 1990, see entire document; 1449, #BI). Claim 20 is drawn to VLA-4-specific antibodies in a pharmaceutical composition. VLA-4-specific antibodies, including the claimed HP2/1 antibody, are taught in the reference as well as their use in several assays including adhesion inhibition assays and flow cytometry. The antibodies were suspended in PBS/BSA/HS for the flow cytometry assays and it is not clear what diluent was employed in the adhesion inhibition assays. However, a pharmaceutically acceptable carrier such as PBS was well known in the art as solvent for immunoglobulins for storage as well as immunoassays. Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

It is the burden of the applicant to show the unobvious difference between the claimed and disclosed antibody compositions. See In re Best, 195 USPQ 430, 433 (CCPA 1977) and In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983).

33. Claim 20 is rejected under 35 U.S.C. § 102(e) as being anticipated by Hession et al. (U.S. Patent No. 5,272,263). Hession et al. teach the VLA-4-specific antibodies including HP1/3 (column 30) and the use of such antibodies in various assays and in therapy (see columns 12-14, for example). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced antibodies. A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

34. Claims 1-21 are rejected under 35 U.S.C. § 103 as being unpatentable over Osborn (Cell, 1990) and Weller et al. (PNAS, 1991; 1449, #AH) in view of Wegner et al. (EP 387701), Hession et al. (U.S. Patent No. 5,272,263) and Gundel et al. (J. Allergy Clin. Immunol., 1990) and Sanchez-Madrid et al. (Eur. J. Immunol., 1986; 1449, CH).

Claims 1-21 are drawn to inhibiting asthma with VLA-4-specific inhibitors including monoclonal antibodies, soluble mediators such as VCAM-1 and the like.

Osborn teaches the potential of interfering with leukocyte-endothelium interactions with adhesion-blocking reagents such as antibodies or alternatively, small peptides or other molecules that will bind adhesion molecules (receptor or ligand) as a therapeutic means to reduce or to prevent leukocyte-mediated disease such as asthma (page 6). There is no evidence that the method of use described in the instant claims would differ in an unexpected manner from those described in the reference. Osborn teaches the invention substantially as claimed to use anti-VLA-4 antibodies to treat asthma therapeutically. Osborn does not exemplify the therapeutic use of anti-VLA-4 monoclonal antibodies as a method of treating asthma.

Weller et al. teach that the HP1/2 and HP2/1 anti-VLA-4 monoclonal antibodies inhibit human eosinophil adherence to VCAM-1- (VLA-4 ligand) transfected CHO cells and HP2/1 blocks eosinophil adhesion to stimulated endothelial cells (pages 7431-7432). There is no distinguishable difference between HP2/1 and HP1/2 monoclonal antibodies since they recognize the same VLA-4 B1 epitope. Weller also teaches that monoclonal antibodies which specifically bind ELAM-1 (BB11) or CD18 (60.3) partially blocked eosinophil adherence to stimulated endothelial cells and that the combination of these anti-adhesion molecule antibodies produced greater inhibition of eosinophil adherence (pages 7431-7432, figure 3). Weller et al. teach that such monoclonal antibodies could be highly effective in inhibiting eosinophil recruitment in vivo including as a treatment for asthma (pages 7432-7433). Applicant's claims are essentially met by this reference. Weller et al. does not exemplify the therapeutic use of anti-VLA-4 monoclonal antibodies as a method of treating asthma.

Gundel et al. teach the correlation between eosinophils and their mediators and the onset and maintenance of airway hyperresponsiveness in primates (see Abstract).

Wegner et al. teaches attenuating cellular adhesion of eosinophils to lung endothelial cells by another adhesion blocking reagent, monoclonal antibodies which specifically bind ICAM-1 (a member of the CD18 family of adhesion molecules) as an in vivo treatment for asthma in cynomologous monkeys. Leukocyte adhesion is required for both migration and as a prerequisite for cytotoxic injury (page 14, lines 35-44). Wegner et al. also teaches the use of biologically active forms of monoclonal antibodies which bind adhesion molecules and/or adhesion receptor/ligand molecules or glycoprotein fragments thereof as therapeutic reagents with respect to CD18/ICAM-1. In addition to teaching analogous therapeutic agents, such antagonists may be administered alone or in combination with other antagonists including adhesion based antagonists. ((pages 6-13). Wegner et al. also teach

Hession et al. teach the role of adhesion molecules including the instant VLA, VCAM, ELAM and ICAM in leukocyte adhesion and infiltration of inflammation. The procedures for preparing of VLA-4-specific antibodies (column 30), soluble adhesion proteins (column 13, lines 47-61 and columns 31-32, Example XV) and the screening procedures for adhesion inhibitors (column 31, Example XIV).

Sanchez-Madrid et al. exemplify the production of anti-VLA-4 monoclonal antibodies which includes some the preferred embodiments of the instant invention including HP1/2, HP2/1 and HP2/4 of the present invention (see claims 3, 13, 16, 21). These VLA-4 antibodies have specificity for the α4 component of VLA-4.

The limitations of the therapeutic methods of administration and dosage of antibodies cited in the instant claims 2,3,6,7,8,17,18 and 19 as the preferred embodiments were routine and obvious in the art to ordinary artisan at the time the invention was made. The limitations of art-known methods as preferred embodiments on the preparation of biologically active fragments of antibodies as indicated by the instant claims 5, 13, 14 and 16 are routine and obvious in the art. Furthermore, both Wegner et al. and Hession et al. provide evidence for this.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Osborn and Weller et al. to that of Wegner et al., Gundel et al. and Hession et al. and to be motivated to practice the methods claimed for treating asthma therapeutically with anti-VLA-4 monoclonal antibodies because anti-VLA-4 antibodies do block eosinophil adherence to endothelium which leads to asthma. Therefore, then ordinary artisan would have employed inhibitors of VLA/VCAM-mediated adhesion as a means to attenuation leukocyte-dependent including eosinophil-dependent

infiltration and subsequent damage associated with asthma. Such VLA/VCAM inhibitors were available at the time the invention was made and were suggested as therapeutic agents to treat asthma.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

35. No claim is allowed.

36. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Margaret Parr can be reached on (703) 308-2454. The fax phone number for Group 1800 is (703) 305-3014 or (703) 308-4227. The fax phone number for Art Unit 1806 is is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

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Patent Examiner
Group 1800
September 28, 1995